CORPORATE SOURCE: Institute of Toxicology, University of Zurich, Switzerland.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1993 Aug 16) 194 (3) 1074-83.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199309
ENTRY DATE: Entered STN: 19931001
Last Updated on STN: 19980206
Entered Medline: 19930915

AB The binding properties of several active and inactive cyclosporins to the major intracellular receptor proteins, cyclophilin A and B, as well as the interaction with the phosphatase calcineurin were investigated by ELISA and by means of a photoaffinity labeled probe (PL-CS). Binding to recombinant human cyclophilin A and B was rapid and saturable, and correlated with the in vitro immunosuppressive activity of cyclosporin derivatives. In the presence of cyclophilin A or B and calcium cyclosporin binds specifically to purified bovine calcineurin. PL-CS labeled only the calcineurin A subunit, but not the B subunit or calmodulin. **Calcineurin** A binding was competed by active (CsA, CsG or CsM), but not inactive (CsH, CsF) derivatives or the structurally unrelated **macrolide** immunosuppressant FK506. Ternary complexes containing equimolar ratios of cyclophilin A or B, PL-CS and calcineurin were resolved by chemical-crosslinking. The formation of these complexes was apparently specific, calcium-, but not calmodulin-dependent, and only inhibited by active cyclosporins. In vivo labelling of Jurkat T-cells revealed, that cyclophilin A and calcineurin A are the main labeled proteins, which form complexes in the presence of active cyclosporin. Thus, we demonstrate directly, that active cyclosporins have two recognition sites, which allow the in vivo recognition of cyclophilins and calcineurin A.

L17 ANSWER 15 OF 19 MEDLINE
ACCESSION NUMBER: 93351328 MEDLINE
DOCUMENT NUMBER: 93351328 PubMed ID: 7688670
TITLE: Cyclosporine- and FK506-induced sympathetic activation correlates with calcineurin-mediated inhibition of T-cell signaling.
AUTHOR: Lyson T; Ermel L D; Belshaw P J; Alberg D G; Schreiber S L; Victor R G
CORPORATE SOURCE: Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas 75235-9034.
CONTRACT NUMBER: R0-1 HL-44010 (NHLBI)
SOURCE: CIRCULATION RESEARCH, (1993 Sep) 73 (3) 596-602.
Journal code: 0047103. ISSN: 0009-7330.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199309
ENTRY DATE: Entered STN: 19931001
Last Updated on STN: 19980206
Entered Medline: 19930910

AB Cyclosporine A (CsA)-induced hypertension appears to be caused in part by neurogenic vasoconstriction, but the mechanism by which CsA activates the sympathetic nervous system is unknown. In T lymphocytes, the cellular target of CsA and the **macrolide** immunosuppressant FK506 (as complexes with their endogenous cytoplasmic receptors, or immunophilins) is the Ca(2+)-calmodulin-dependent phosphatase **calcineurin**. The presence of calcineurin and its colocalization with immunophilin in the brain led us to hypothesize that the phosphatase also mediates CsA-induced sympathetic activation. We now report that sympathetic activity and arterial pressure in rats are increased not only by CsA but also by FK506, which is structurally unrelated to CsA but inhibits the same calcineurin-sensitive T-cell signaling pathway. In contrast, sympathetic activity and blood pressure are not increased by rapamycin, which forms an immunophilin complex that does not bind calcineurin. Furthermore, CsA- and FK506-induced sympathetic activation is attenuated for drug analogues

possessing modest changes in molecular structure in a way that closely parallels the ability of each analogue to inhibit calcineurin-mediated T-cell signaling. These results implicate an important role for extralymphoid (ie, neuronal) calcineurin in mediating immunosuppressive drug toxicity.

L17 ANSWER 16 OF 19 MEDLINE
ACCESSION NUMBER: 94159124 MEDLINE
DOCUMENT NUMBER: 94159124 PubMed ID: 7509460
TITLE: The immunosuppressive drugs cyclosporin A and FK506 inhibit calcineurin phosphatase activity and gene transcription mediated through the cAMP-responsive element in a nonimmune cell line.
AUTHOR: Schwaninger M; Blume R; Oetjen E; Knepel W
CORPORATE SOURCE: Abteilung Biochemische Pharmakologie, Zentrum Pharmakologie und Toxikologie, Universitat Gottingen, Germany.
SOURCE: NAUNYN-SCHMIEDEBERGS ARCHIVES OF PHARMACOLOGY, (1993 Nov) 348 (5) 541-5.
Journal code: 0326264. ISSN: 0028-1298.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199403
ENTRY DATE: Entered STN: 19940406
Last Updated on STN: 19990129
Entered Medline: 19940328

AB Cyclosporin A and the **macrolide** tacrolimus (FK506) are powerful immunosuppressive drugs that in T cells inhibit the calcium/calmodulin-dependent phosphatase **calcineurin** thereby preventing the activation of T-cell-specific transcription factors, such as NF-AT, involved in lymphokine gene expression. While this may explain, at least in part, the mechanism of cyclosporin A/FK506 immunosuppression, additional mechanisms have to be invoked in order to explain the pharmacological properties and toxic effects of these drugs, such as nephrotoxicity and neurotoxicity. We have studied the effects of cyclosporin A and FK506 on calcineurin phosphatase activity and gene transcription mediated by the cAMP-responsive element (CRE), a binding site of the ubiquitous transcription factor CREB. A reporter gene was placed under the transcriptional control of the CRE of the rat glucagon gene and transiently transfected into the glucagon-expressing cell line alpha TC2. Cyclosporin A and FK506 inhibited depolarization-induced gene transcription in a concentration-dependent manner (IC50 of about 1 nM and 30 nM for FK506 and cyclosporin A, respectively). Both cyclosporin A and FK506 inhibited calcineurin phosphatase activity at drug concentrations that inhibited gene transcription. The FK506 analogue rapamycin had no effect on calcineurin activity and gene transcription, but excess concentrations of rapamycin prevented the effects of FK506 on both calcineurin activity and gene transcription. These results support the notion that the interaction of drug-immunophilin complexes with calcineurin may be the molecular basis of cyclosporin A/FK506-induced inhibition of CREB/CRE-mediated gene transcription. The ability to interfere with CREB/CRE-mediated gene transcription represents a novel mechanism of cyclosporin A/FK506 action which may underlie pharmacological effects and toxic manifestations of these potent immunuosuppressive drugs.

L17 ANSWER 17 OF 19 MEDLINE
ACCESSION NUMBER: 93326130 MEDLINE
DOCUMENT NUMBER: 93326130 PubMed ID: 7687433
TITLE: Comparison of conformations of cyclosporin A and **macrolide** FK506 fragments: localization of putative binding sites with phosphatase **calcineurin**.
AUTHOR: Denesyuk A I; Korpela T; Lundell J; Sara R; Zav'yalov V P
CORPORATE SOURCE: Institute of Immunology, Lyubuchany, Russia.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1993 Jul 15) 194 (1) 280-6.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199308
ENTRY DATE: Entered STN: 19930826
Last Updated on STN: 19980206
Entered Medline: 19930817

AB The three-dimensional structures of two immunosuppressants, cyclosporin A and macrolide FK506, were compared. The sites N-methylglycine3-N-methylleucine4 and valine5-N-methylleucine6 of cyclosporin A were found to be similar to each other (the root-mean-square value was 0.29 A for six reference points of the main chain) and also to the site C17-C22 of FK506 (the root-mean-square values were 0.33 A and 0.13 A, respectively). We suggest these fragments of cyclosporin A and FK506 make a major contribution to the interaction of the immunosuppressants with the phosphatase calcineurin.

L17 ANSWER 18 OF 19 MEDLINE
ACCESSION NUMBER: 92159009 MEDLINE
DOCUMENT NUMBER: 92159009 PubMed ID: 1371354
TITLE: Neisseria meningitidis encodes an FK506-inhibitable rotamase.
AUTHOR: Sampson B A; Gotschlich E C
CORPORATE SOURCE: Laboratory of Bacterial Pathogenesis and Immunology, Rockefeller University, New York, NY 10021-6399.
CONTRACT NUMBER: AI26558 (NIAID)
S07RR07065 (NCRR)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1992 Feb 15) 89 (4) 1164-8.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199203
ENTRY DATE: Entered STN: 19920410
Last Updated on STN: 19960129
Entered Medline: 19920323

AB Eukaryotic peptidyl-prolyl cis-trans isomerases (rotamases) fall into two classes, the **cyclophilins** inhibited by cyclosporin A and the FK506-binding proteins inhibited by the **macrolide** antibiotic FK506. In prokaryotes homologs of cyclophilins have been identified and found to have rotamase activity. Sequence similarities have been noted between FK506-binding proteins and gene products in a number of bacterial species, but whether these bacterial proteins have rotamase activity is not known. Using the polymerase chain reaction, we have cloned and sequenced a homolog of an FK506-binding protein from Neisseria meningitidis and expressed the gene product as a fusion protein with maltose-binding protein. The fusion protein was purified by affinity chromatography. By measuring the rate of chymotrypsin cleavage of the substrate succinyl-Ala-Ala-Pro-Phe p-nitroanilide, we found that the fusion protein had rotamase activity comparable to that of human FK506-binding protein. This rotamase activity was inhibited by FK506.

L17 ANSWER 19 OF 19 MEDLINE
ACCESSION NUMBER: 92313325 MEDLINE
DOCUMENT NUMBER: 92313325 PubMed ID: 1820035
TITLE: Slow conformational changes in protein folding can be accelerated by enzymes.
AUTHOR: Bang H; Fischer G
CORPORATE SOURCE: Martin-Luther-Universitat Halle-Wittenberg, Institut fur Biochemie.
SOURCE: BIOMEDICA BIOCHIMICA ACTA, (1991) 50 (10-11) S137-42.
Journal code: 8304435. ISSN: 0232-766X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199207
ENTRY DATE: Entered STN: 19920807
Last Updated on STN: 19980206
Entered Medline: 19920724

AB In vitro protein folding is a spontaneous process that is driven by a small difference in Gibbs free energy between the native and unfolded states. The information required for correct folding should be entirely encoded in the amino acid sequence of the protein, although increasing evidence exist that proteins participate in cellular folding events. Isomerization of Xaa-Pro peptide bonds is thought to represent some slow steps of folding kinetics. This type of molecular reorganization have to be important in cellular folding due to the different isomeric states in proteins. Peptidyl-prolyl-cis/trans-isomerase (PPIase) catalyzes some, but not all, proline-limited slow folding reactions. On the other hand, the amino acid sequence of 17,8 kD PPIase from pig kidney is identical with cyclophilin (Cyp) that is the major cellular binding protein for the immunosuppressive drug cyclosporin A (CsA). The connection between enzyme catalyzed cis/trans isomerization, protein folding and immunosuppression is still unknown. PPIases of the cyclophilin type are found in most organisms and in various subcellular compartments. Recently a second family of PPIases has been discovered. These small proteins are structurally related to the **cyclophilins**; yet they bind with a high affinity to another immunosuppressive drug, the **macrolide** FK 506. Although it seems to be logical to ascribe the enzymatic activity of these proteins to a catalytic role in the folding of proteins within the cell other possibilities must also be considered and are discussed.

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L17 ANSWER 1 OF 19 MEDLINE
ACCESSION NUMBER: 2003162936 MEDLINE
DOCUMENT NUMBER: 22544471 PubMed ID: 12656618
TITLE: Sanglifehrin-cyclophilin interaction: degradation work, synthetic macrocyclic analogues, X-ray crystal structure, and binding data.
AUTHOR: Sedrani Richard; Kallen Jorg; Martin Cabrejas Luisa M; Papageorgiou Charles D; Senia Francesco; Rohrbach Stefan; Wagner Dieter; Thai Binh; Jutzi Eme Anne-Marie; France Julien; Oberer Lukas; Rihs Grety; Zenke Gerhard; Wagner Jurgen
CORPORATE SOURCE: Transplantation Research, Novartis Pharma AG, S-507.312, CH-4002 Basel, Switzerland.
SOURCE: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, (2003 Apr 2) 125 (13) 3849-59.
Journal code: 7503056. ISSN: 0002-7863.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20030409
Last Updated on STN: 20030524
Entered Medline: 20030523

AB Sanglifehrin A (SFA) is a novel immunosuppressive natural product isolated from Streptomyces sp. A92-308110. SFA has a very strong affinity for cyclophilin A (IC(50) = 6.9 +/- 0.9 nM) but is structurally different from cyclosporin A (CsA) and exerts its immunosuppressive activity via a novel mechanism. SFA has a complex molecular structure consisting of a 22-membered macrocycle, bearing in position 23 a nine-carbon tether terminated by a highly substituted spirobicyclic moiety. Selective oxidative cleavage of the C(26)=C(27) exocyclic double bond affords the spirolactam containing fragment 1 and macrolide 2. The affinity of 2 for cyclophilin (IC(50) = 29 +/- 2.1 nM) is essentially identical to SFA, which indicates that the interaction between SFA and cyclophilin A is mediated exclusively by the macrocyclic portion of the molecule. This observation was confirmed by the X-ray crystal structure resolved at 2.1 A of **cyclophilin** A complexed to **macrolide** 16, a close analogue of 2. The X-ray crystal structure showed that **macrolide** 16 binds to the same deep hydrophobic pocket of **cyclophilin** A as CsA. Additional valuable details of the structure-activity relationship were obtained by two different chemical approaches: (1) degradation work on macrolide 2 or (2) synthesis of a library of macrolide analogues using the ring-closing metathesis reaction as the key step. Altogether, it appears that the complex macrocyclic fragment of SFA is a highly optimized combination of multiple functionalities including an (E,E)-diene, a short polypropionate fragment, and an unusual tripeptide unit, which together provide an extremely strong affinity for cyclophilin A.

L17 ANSWER 2 OF 19 MEDLINE
ACCESSION NUMBER: 2002698005 MEDLINE
DOCUMENT NUMBER: 22347227 PubMed ID: 12459545
TITLE: The macrolide immunosuppressants in dermatology: mechanisms of action.
AUTHOR: Marsland Alexander M; Griffiths Christopher E M
CORPORATE SOURCE: Dermatology Centre, University of Manchester School of Medicine, Hope Hospital, United Kingdom.. sacha.marsland@virgin.net
SOURCE: EUROPEAN JOURNAL OF DERMATOLOGY, (2002 Nov-Dec) 12 (6) 618-22. Ref: 27
Journal code: 9206420. ISSN: 1167-1122.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20021217
Last Updated on STN: 20030328
Entered Medline: 20030327

AB Macrolides are xenobiotics, produced by soil fungi, which have immunosuppressant properties. They will probably revolutionise the treatment of inflammatory dermatoses. This article outlines the context and putative mechanisms of action of this novel class of drugs. Cyclosporin, and the structurally distinct **macrolides** tacrolimus and pimecrolimus (an ascomycin derivative), modulate immune-cell function by inhibiting **calcineurin**-dependent dephosphorylation-activation of specific nuclear factors, thus preventing transcription of pro-inflammatory cytokines. The macrolide rapamycin (sirolimus) acts by abrogating Target of Rapamycin, a key signalling protein that controls activation of a number of proteins which direct progression of the cell cycle in response to pro-inflammatory cytokines. Tacrolimus and pimecrolimus are small enough molecules to penetrate skin and are available in topical formulations. "Skin-specific" pimecrolimus seems not to cause systemic immunosuppression when given orally. Neither topical tacrolimus nor pimecrolimus are capable of producing skin atrophy. Sirolimus has anti-angiogenic properties that may be beneficial to the treatment of psoriasis and perhaps skin cancer.

L17 ANSWER 3 OF 19 MEDLINE
ACCESSION NUMBER: 2001320068 MEDLINE
DOCUMENT NUMBER: 21286462 PubMed ID: 11390463
TITLE: Sanglifehrin A, a novel cyclophilin-binding compound showing immunosuppressive activity with a new mechanism of action.
AUTHOR: Zenke G; Strittmatter U; Fuchs S; Quesniaux V F; Brinkmann V; Schuler W; Zurini M; Enz A; Billich A; Sanglier J J; Fehr T
CORPORATE SOURCE: Transplantation Research, Core Technology, and Nervous System Research, Novartis Pharma, Basel, Switzerland.. gerhard.zenke@pharma.novartis.com
SOURCE: JOURNAL OF IMMUNOLOGY, (2001 Jun 15) 166 (12) 7165-71. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010827
Last Updated on STN: 20010827
Entered Medline: 20010823

AB We report here on the characterization of the novel immunosuppressant Sanglifehrin A (SFA). SFA is a representative of a class of **macrolides** produced by actinomycetes that bind to **cyclophilin** A (CypA), the binding protein of the fungal cyclic peptide cyclosporin A (CsA). SFA interacts with high affinity with the CsA binding side of CypA and inhibits its peptidyl-prolyl isomerase activity. The mode of action of SFA is different from known immunosuppressive drugs. It has no effect on the phosphatase activity of calcineurin, the target of the immunosuppressants CsA and FK506 when complexed to their binding proteins CypA and FK binding protein, respectively. Moreover, its effects are independent of binding of cyclophilin. SFA inhibits alloantigen-stimulated T cell proliferation but acts at a later stage than CsA and FK506. In contrast to these drugs, SFA does not affect IL-2 transcription or secretion. However, it blocks IL-2-dependent proliferation and cytokine production of T cells, in this respect resembling rapamycin. SFA inhibits the proliferation of mitogen-activated B cells, but, unlike rapamycin, it has no effect on CD154/IL-4-induced Ab synthesis. The activity of SFA is also different from that of other known late-acting immunosuppressants, e.g., mycophenolate mofetil or brequinar, as it does not affect de novo purine and pyrimidine biosynthesis. In summary, we have identified a novel immunosuppressant, which represents, in addition to CsA, FK506 and rapamycin, a fourth class of immunophilin-binding metabolites with a new, yet undefined mechanism of action.

L17 ANSWER 4 OF 19 MEDLINE
ACCESSION NUMBER: 2001387497 MEDLINE
DOCUMENT NUMBER: 21336953 PubMed ID: 11443573
TITLE: mTOR inhibitors: an overview.
AUTHOR: Neuhaus P; Klupp J; Langrehr J M
CORPORATE SOURCE: Department of Surgery, Charite Virchow, Berlin, Germany.. chirurgie@charite.de
SOURCE: LIVER TRANSPLANTATION, (2001 Jun) 7 (6) 473-84. Ref: 119
Journal code: 100909185. ISSN: 1527-6465.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20011001
Last Updated on STN: 20011001
Entered Medline: 20010927

AB Inhibitors of the mammalian target of rapamycin are a new class of immunosuppressants. In contrast to other **macrolides**, such as tacrolimus and cyclosporine A, they do not inhibit **calcineurin** and thus signal I of T-cell activation. By inhibiting signal III, the mechanism of action and side effects of sirolimus (rapamycin) and its derivative RAD are distinct from other immunosuppressants. Reports of synergism with cyclosporine A and tacrolimus in preclinical and clinical studies, avoidance of nephrotoxicity, and possible treatment or prevention of chronic allograft rejection are leading to high expectations for this new class of immunosuppressants. Furthermore, studies evaluating tolerance induction are being conducted. This review summarizes preclinical and clinical results published to date and exploits the future value of sirolimus and RAD for clinical transplantation.

L17 ANSWER 5 OF 19 MEDLINE
ACCESSION NUMBER: 1999408448 MEDLINE
DOCUMENT NUMBER: 99408448 PubMed ID: 10480571
TITLE: Sanglifehrins A, B, C and D, novel cyclophilin-binding compounds isolated from Streptomyces sp. A92-308110. II. Structure elucidation, stereochemistry and physico-chemical properties.
AUTHOR: Fehr T; Kallen J; Oberer L; Sanglier J J; Schilling W
CORPORATE SOURCE: Novartis Pharma Inc., Research, Department of Core Technology, Basel, Switzerland.
SOURCE: JOURNAL OF ANTIBIOTICS, (1999 May) 52 (5) 474-9.
Journal code: 0151115. ISSN: 0021-8820.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991012
Last Updated on STN: 19991012
Entered Medline: 19990927

AB A novel class of **macrolides**, the sanglifehrins, was discovered by screening of actinomycete strains with a **cyclophilin**-binding assay. The chemical structures and absolute stereochemistries of the sanglifehrins A, B, C and D were determined unambiguously by NMR-techniques and by X-ray crystallography of the complex with cyclophilin A. Sanglifehrin A consists of a 22-membered macrocycle containing a tripeptide subunit and features in position 23 a chain of nine carbon atoms bearing a spirocyclic substituent. Sanglifehrins A and B are genuine metabolites whereas sanglifehrins C and D are artefacts.

L17 ANSWER 6 OF 19 MEDLINE
ACCESSION NUMBER: 1999408447 MEDLINE
DOCUMENT NUMBER: 99408447 PubMed ID: 10480570
TITLE: Sanglifehrins A, B, C and D, novel cyclophilin-binding compounds isolated from Streptomyces sp. A92-308110. I. Taxonomy, fermentation, isolation and biological activity.
AUTHOR: Sanglier J J; Quesniaux V; Fehr T; Hofmann H; Mahnke M;

Memmert K; Schuler W; Zenke G; Gschwind L; Maurer C; Schilling W

CORPORATE SOURCE: Novartis Pharma Inc., Research, Departments of Core Technology and Transplantation, Basel, Switzerland.

SOURCE: JOURNAL OF ANTIBIOTICS, (1999 May) 52 (5) 466-73.
Journal code: 0151115. ISSN: 0021-8820.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991012
Last Updated on STN: 19991012
Entered Medline: 19990927

AB A novel class of **macrolides** for which the name sanglifehrins is proposed, has been discovered from actinomycete strains based on their high affinity binding for **cyclophilin** A (CypA), an immunophilin originally identified as a cytosolic protein binding cyclosporin A (CsA). The sanglifehrins were produced by Streptomyces sp. A92-308110. They were isolated and purified by extraction and several chromatographic, activity-guided steps. Sanglifehrins A and B exhibit a 10 to approximately 20 fold higher affinity for CypA than CsA, whereas the affinity of sanglifehrins C and D for CypA is comparable to that of CsA. Sanglifehrins exhibit a lower immunosuppressive activity than CsA when tested in the mixed lymphocyte reaction. Their in vitro activity indicates that they belong to a novel class of immunosuppressants.

L17 ANSWER 7 OF 19 MEDLINE

ACCESSION NUMBER: 1999339295 MEDLINE
DOCUMENT NUMBER: 99339295 PubMed ID: 10412950

TITLE: Immunosuppressant inhibition of P-glycoprotein function is independent of drug-induced suppression of peptide-prolyl isomerase and calcineurin activity.

AUTHOR: Mealey K L; Barhoumi R; Burghardt R C; McIntyre B S; Sylvester P W; Hosick H L; Kochevar D T

CORPORATE SOURCE: Department of Veterinary Physiology and Pharmacology, College of Veterinary Medicine, Texas A&M University, College Station 77843, USA.

CONTRACT NUMBER: CA 68001 (NCI)
SOURCE: CANCER CHEMOTHERAPY AND PHARMACOLOGY, (1999) 44 (2) 152-8.
Journal code: 7806519. ISSN: 0344-5704.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990806
Last Updated on STN: 19990806
Entered Medline: 19990729

AB PURPOSE: P-glycoprotein is a 170-kDa plasma membrane multidrug transporter that actively exports cytotoxic substances from cells. Overexpression of P-glycoprotein by tumor cells is associated with a multidrug-resistant phenotype. Immunosuppressive agents such as cyclosporins and macrolides, have been shown to attenuate P-glycoprotein activity. However, the mechanism by which some immunosuppressants inhibit P-glycoprotein function has not been determined. Since cyclosporin and **macrolide** immunosuppressants inhibit **calcineurin** (CaN) phosphatase and FKBP12 peptideprolyl isomerase (FKBP12 PPI) activity, studies were conducted to determine if these effects are directly related to the inhibitory effects these immunosuppressants have on P-glycoprotein function. METHODS: Western blot analysis was performed to assess CaN and FKBP12 protein levels in P-glycoprotein-negative (MCF-7) and -positive (MCF-7/Adr) breast cancer cell lines. P-glycoprotein function was determined by intracellular doxorubicin accumulation and/or cytotoxicity assays before and after CaN and FKBP12 were independently inhibited by pharmacological antagonists. RESULTS: CaN and FKBP12 levels were similar in MCF-7 and MCF-7/Adr cells. P-glycoprotein function was not affected by treatment of P-glycoprotein-expressing MCF-7/Adr cells with CaN and FKBP12 antagonists. CONCLUSIONS: These results demonstrate that the inhibitory effects of immunosuppressive agents on P-glycoprotein function are

independent of CaN or FKBP12 PPI activity.

L17 ANSWER 8 OF 19 MEDLINE
ACCESSION NUMBER: 1999086028 MEDLINE
DOCUMENT NUMBER: 99086028 PubMed ID: 9870481
TITLE: Enhancement of human platelet aggregation and secretion induced by rapamycin.
AUTHOR: Babinska A; Markell M S; Salifu M O; Akoad M; Ehrlich Y H; Kornecki E
CORPORATE SOURCE: Department of Cell Biology and Anatomy, SUNY Health Science Center at Brooklyn, New York 11203, USA.
SOURCE: NEPHROLOGY, DIALYSIS, TRANSPLANTATION, (1998 Dec) 13 (12) 3153-9.
Journal code: 8706402. ISSN: 0931-0509.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990326
Last Updated on STN: 19990326
Entered Medline: 19990318

AB BACKGROUND: Rapamycin is a new immunosuppressive drug of the macrolide type. Despite binding to one of the FK-binding proteins as the initial step in intracellular action, further effects differ from those of the other fungally derived macrolides, cyclosporine and tacrolimus. We have previously demonstrated an enhancement of agonist-mediated platelet activation by cyclosporine and tacrolimus which was associated with increased phosphorylation of two intracellular platelet proteins, p20 and p40. Because rapamycin utilizes the same class of binding proteins as tacrolimus, but its action is not associated with the inhibition of calcineurin, we postulated that if the stimulatory effect of cyclosporine or tacrolimus was due to calcineurin inhibition, rapamycin should not affect platelets in a similar fashion. METHODS: Normal, washed human platelets were treated with various concentrations of rapamycin (from ng to microg/ml), and pre-incubated at 37 degrees C with rapamycin for various periods (1-30 min). Several platelet functional parameters were measured in samples treated with rapamycin and these parameters were compared with control platelet samples treated with the vehicle for the same period. Platelet aggregations following exposure to ADP or to the thrombin equivalent, TRAP-6, were measured as changes in optical transmission in a Chronolog lumi-aggregometer. Each experiment was repeated at three or more times and the mean results were used for statistical comparison. RESULTS: Rapamycin-treated platelets demonstrated an increase in their dose- and time-dependent sensitivity to ADP, resulting in a significantly enhanced primary wave of ADP-induced platelet aggregation followed by a secondary wave of aggregation, indicative of granule secretion. Furthermore, rapamycin-treated platelets showed significantly enhanced sensitivity to TRAP-6 as demonstrated by an increase in the initial velocity of aggregation, an increase in their maximal extent of aggregation and an enhancement of granular ATP secretion. Concentrations of rapamycin in the ng range, as well as short pre-incubation times (within min), were sufficient to cause significant enhancement of agonist-induced platelet aggregation and secretion ($P < 0.001$) as compared with their vehicle controls. CONCLUSIONS: Rapamycin significantly potentiates agonist-induced platelet aggregation in a time- and dose-dependent manner. As these findings are similar to those observed with the other fungal **macrolides**, we hypothesize that inhibition of **calcineurin** may not be necessary for the increase in intracellular protein phosphorylation observed following exposure of platelets to cyclosporine or tacrolimus. Whether the rapamycin-induced enhancement of sensitivity to agonists and platelet hyperaggregability explains the thrombocytopenia observed in patients when high doses of rapamycin are administered in the clinical setting, and whether these effects are synergistic with cyclosporine, are questions which remain to be investigated.

L17 ANSWER 9 OF 19 MEDLINE
ACCESSION NUMBER: 97256352 MEDLINE
DOCUMENT NUMBER: 97256352 PubMed ID: 9101762

TITLE: Conformational polymorphism in peptidic and nonpeptidic drug molecules.
AUTHOR: Taylor P; Mikol V; Kallen J; Burkhard P; Walkinshaw M D
CORPORATE SOURCE: Structural Biochemistry Group, Department of Biochemistry, The University of Edinburgh, UK.
SOURCE: BIOPOLYMERS, (1996) 40 (5) 585-92.
Journal code: 0372525. ISSN: 0006-3525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970424
Last Updated on STN: 19990129
Entered Medline: 19970417

AB **Macrolide** ligands that bind FK506 binding proteins and cyclosporins that a bind **cyclophilins** are chemically dissimilar but can share a number of structural and biological properties. Both families of ligands have very different conformations in the free state compared to those adopted when complexed with their binding protein. These transformations involve twisting from cis to trans about specific amide bonds, which result in significant changes in the hydrogen-bonding capabilities of the molecular surfaces. The three-dimensional structure of a new cyclosporin-like ligand (SDZ214 - 103) is described in the free crystalline state and bound to cyclophilin, and is shown to have a very different conformation from cyclosporin A in the free crystal, but a very similar conformation when bound to cyclophilin.

L17 ANSWER 10 OF 19 MEDLINE
ACCESSION NUMBER: 96418970 MEDLINE
DOCUMENT NUMBER: 96418970 PubMed ID: 8821755
TITLE: Only 'de novo' long-term depression (LTD) in the rat hippocampus in vitro is blocked by the same low concentration of FK506 that blocks LTD in the visual cortex.
AUTHOR: Hodgkiss J P; Kelly J S
CORPORATE SOURCE: Department of Pharmacology, University of Edinburgh, Scotland, UK.
SOURCE: BRAIN RESEARCH, (1995 Dec 24) 705 (1-2) 241-46.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19980206
Entered Medline: 19961106

AB It has been proposed that the long-term depression (LTD) seen following low frequency stimulation (LFS) in the rat hippocampus involves calcineurin. We have tested this by examining the effect of FK506, a **macrolide** which blocks **calcineurin** at nanomolar concentrations, on synaptic transmission in the rat hippocampal slice at a concentration of 1 microM which has been shown to block LTD in the visual cortex. The effect of FK506 on long-term potentiation (LTP) and spontaneous transmitter release was also studied. The magnitude of LTD induced by LFS was 16.7 +/- 2.4% in control which was not significantly different from the 22.3 +/- 3.0% seen in the same preparations after exposure to FK506 for 25-30 min. In contrast the magnitude of LTD induced 'de novo' in preparations exposed to FK506 was significantly reduced. FK506 had no significant effect on LTP, miniature EPSP frequency, miniature EPSP amplitude, resting membrane potential or input resistance. These results, therefore, support the hypothesis that calcineurin is involved in 'de novo' LTD but it appears that an event is triggered by LFS whereby FK506-insensitive LTD can subsequently be activated by a second episode of LFS.

L17 ANSWER 11 OF 19 MEDLINE
ACCESSION NUMBER: 94242071 MEDLINE
DOCUMENT NUMBER: 94242071 PubMed ID: 7514409

TITLE: Demonstration of ternary immunophilin-**calcineurin** complexes with the immunosuppressants cyclosporin and **macrolide** FK506.
AUTHOR: Woerly G; Weber E; Ryffel B
CORPORATE SOURCE: Institute of Toxicology, University of Zurich, Switzerland.
SOURCE: BIOCHEMICAL PHARMACOLOGY, (1994 Apr 20) 47 (8) 1435-43. Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 19940621
Last Updated on STN: 19980206
Entered Medline: 19940614

AB The specificity of cyclosporin A (CsA) binding to the major intracellular receptor proteins, cyclophilin A and B, as well as the interaction of CsA with the phosphatase calcineurin were investigated. Binding of photoaffinity-labeled CsA (PL-CS), a photoaffinity probe of CsA, to recombinant human cyclophilin A and B is saturable and specific. Non-specific PL-CS binding to calcineurin is observed in the absence of cyclophilin and calmodulin. In the presence of cyclophilin, cyclosporin-calcineurin binding becomes specific. Ternary complexes containing an equimolar ratio of cyclophilin A or B, PL-CS and calcineurin are resolved using the chemical-crosslinking technique. The formation of these complexes is specific, calcium- but not calmodulin-dependent, and is only inhibitable by cyclosporins, which bind cyclophilin. The drug-immunophilin complex binds to the calcineurin A subunit. The proteolytic 43 kDa product of calcineurin A retains binding properties, suggesting that the C-terminal domains are not necessary for complex formation. A trimeric complex of FKBP-calcineurin is also formed with FK506, but not with rapamycin. As expected, these complexes are only competed with by homologous derivatives. Chemical crosslinking of photolabeled Jurkat T-cells strongly suggests that drug-calcineurin complexes are of biological relevance.

L17 ANSWER 12 OF 19 MEDLINE
ACCESSION NUMBER: 94347135 MEDLINE
DOCUMENT NUMBER: 94347135 PubMed ID: 7520696
TITLE: Roles of peptidyl-prolyl cis-trans isomerase and calcineurin in the mechanisms of antimalarial action of cyclosporin A, FK506, and rapamycin.
AUTHOR: Bell A; Wernli B; Franklin R M
CORPORATE SOURCE: Department of Structural Biology, Biozentrum of the University of Basel, Switzerland.
SOURCE: BIOCHEMICAL PHARMACOLOGY, (1994 Aug 3) 48 (3) 495-503. Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199409
ENTRY DATE: Entered STN: 19941005
Last Updated on STN: 19990129
Entered Medline: 19940920

AB The immunosuppressive peptide cyclosporin A inhibits the growth of malaria parasites in vitro and in vivo, but little is known about its mechanism of antimalarial action. The immunosuppressive action of cyclosporin A is believed to result from binding of the drug to cyclophilins (intracellular peptidyl-prolyl cis-trans isomerases), and inhibition of the protein phosphatase calcineurin by the cyclosporin A-cyclophilin complex. Two immunosuppressive **macrolides**, FK506 and rapamycin, bind to a distinct isomerase, FKBP12, and the FK506-FKBP complex also inhibits **calcineurin**. Calcineurin itself is apparently involved in signal transduction between the T-cell membrane and nucleus, and its inhibition blocks T-cell activation. Rapamycin inhibits a later step in T-cell proliferation. Peptidyl-propyl cis-trans isomerase activity was detected in extracts of Plasmodium falciparum. It was completely inhibited by concentrations of cyclosporin A above 0.1 microM, but not by FK506 or rapamycin, and probably represented one or more cyclophilins. Comparison

of the antimalarial and anti-isomerase activities of a series of cyclosporin analogues failed to reveal a correlation between the two properties. Cyclosporin A and its more active 8'-oxymethyl-dihydro-derivative, in combination with the cyclophilin-containing P. falciparum extract, inhibited the protein phosphatase activity of bovine calcineurin. Therefore inhibition of a putative P. falciparum calcineurin by a complex of CsA and cyclophilin might be responsible for the antimalarial action of the drug. The most active cyclosporin, however, was a 3'-keto-derivative of cyclosporin D (SDZ PSC-833) which inhibited P. falciparum growth with a 50% inhibitory concentration (IC50) of 0.032 microM (compared with 0.30 microM for cyclosporin A), but was a poor inhibitor of the parasite isomerase. 3'-Keto-cyclosporin D has negligible immunosuppressive activity, but it strongly inhibits the P-glycoprotein of multi-drug resistant mammalian tumour cells. FK506 and rapamycin were also active antimalarials (IC50 of 1.9 and 2.6 microM, respectively) but in the absence of detectable FKBP in P. falciparum extracts, their mechanisms of antimalarial action remain unclear.

L17 ANSWER 13 OF 19 MEDLINE
ACCESSION NUMBER: 93203579 MEDLINE
DOCUMENT NUMBER: 93203579 PubMed ID: 7681074
TITLE: A role for calcineurin in degranulation of murine cytotoxic T lymphocytes.
AUTHOR: Dutz J P; Fruman D A; Burakoff S J; Bierer B E
CORPORATE SOURCE: Center for Cancer Research, Massachusetts Institute of Technology, Cambridge 02139.
CONTRACT NUMBER: CA 14051 (NCI)
PO1-CA 39542 (NCI)
R35-CA 42504 (NCI)
+
SOURCE: JOURNAL OF IMMUNOLOGY, (1993 Apr 1) 150 (7) 2591-8.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930507
Last Updated on STN: 19990129
Entered Medline: 19930420

AB The immunosuppressive drugs cyclosporin A (CsA) and FK506 bind to distinct families of intracellular proteins, cyclophilins, and FK506 binding proteins (FKBP) respectively, termed immunophilins. Immuno-suppressant-immunophilin complexes bind to and inhibit the activity of calcineurin, a calcium-dependent serine/threonine phosphatase. CsA is known to inhibit degranulation in CTL as assessed by N benzyloxylcarbonyl-L-lysine thiobenzyl ester-esterase release assays. We have investigated whether calcineurin phosphatase activity is involved in this degranulation. Both CsA and FK506 are shown to inhibit N benzyloxylcarbonyl-L-lysine thiobenzyl esteresterase release in murine CTL clones induced either by cognate target or by PMA and the calcium ionophore A23187. Inhibition is concentration dependent and is observed at drug concentrations that specifically inhibit cellular calcineurin. The FK506-binding immunophilin FKBP12, as well as calcineurin, are shown to be present in these cells by immunoblotting analysis. Rapamycin, a **macrolide** antibiotic thought to compete with FK506 for binding to common FKBP receptor sites, antagonizes the effects of FK506 on both degranulation and **calcineurin** activity. Neither the degranulation nor the effect of the immunosuppressants is affected by the protein synthesis inhibitor cycloheximide. These observations suggest a role for calcineurin in CTL degranulation. Thus, in addition to its previously described role in lymphokine gene activation, calcineurin also appears to be involved in T cell activation processes which do not require protein synthesis.

L17 ANSWER 14 OF 19 MEDLINE
ACCESSION NUMBER: 93356770 MEDLINE
DOCUMENT NUMBER: 93356770 PubMed ID: 8394698
TITLE: Binding of active cyclosporins to cyclophilin A and B, complex formation with calcineurin A.
AUTHOR: Ryffel B; Woerly G; Murray M; Eugster H P; Car B

L12 ANSWER 5 OF 8 MEDLINE
ACCESSION NUMBER: 95370205 MEDLINE
DOCUMENT NUMBER: 95370205 PubMed ID: 7642551
TITLE: FK506 binding protein mutational analysis. Defining the surface residue contributions to stability of the calcineurin co-complex.
AUTHOR: Futer O; DeCenzo M T; Aldape R A; Livingston D J
CORPORATE SOURCE: Vertex Pharmaceuticals Incorporated, Cambridge, Massachusetts 02139-4211, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Aug 11) 270 (32) 18935-40.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 19950930
Last Updated on STN: 19980206
Entered Medline: 19950918

AB The 12- and 13-kDa **FK506 binding proteins** (FKBP12 and FKBP13) are cis-trans peptidyl-prolyl isomerases that bind the **macrolides** FK506 (Tacrolimus) and rapamycin (Sirolimus). The FKBP12.FK506 complex is immunosuppressive, acting as an inhibitor of the protein phosphatase calcineurin. We have examined the role of the key surface residues of FKBP12 and FKBP13 in calcineurin interactions by generating substitutions at these residues by site-directed mutagenesis. All mutants are active catalysts of the prolyl isomerase reaction, and bind FK506 or rapamycin with high affinity. Mutations at FKBP12 residues Asp-37, Arg-42, His-87, and Ile-90 decrease calcineurin affinity of the mutant FKBP12.FK506 complex by as much as 2600-fold in the case of I90K. Replacement of three FKBP13 surface residues (Gln-50, Ala-95, and Lys-98) with the corresponding homologous FKBP12 residues (Arg-42, His-87, and Ile-90) generates an FKBP13 variant that is equivalent to FKBP12 in its affinity for FK506, rapamycin, and calcineurin. These results confirm the role of two loop regions of FKBP12 (residues 40-44 and 84-91) as part of the effector face that interacts with calcineurin.

MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN
Designated States (Regional): AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
AU 9741672 A Based on WO 9808956
Language, Pages: WO 9808956 (E, 85)

Set	Items	Description
S1	132	((X(W)RAY(W)CRYSTALLOGRAPHY) OR (CRYSTAL(W)STRUCTURE?))(S)-(CYCLOPHILIN OR CALCINEURIN OR FRAP OR FK506(W)BINDING(W)PROT-EIN OR FRB OR FKBP)(S)(FK506 OR CYCLOSPORIN OR RAPAMYCIN)
S2	52	RD (unique items)

```
et      Items   Description
S1      12361   (MACROLIDE(W)BINDING(W)PROTEIN OR FRAP OR FK506(W)BINDING -
             OR CALCINEURIN OR CYCLOPHILIN)
S2         16   S1 (S)HEMATOPOIETIC(W)CELL?
S3          5   RD (unique items)
S4       1031   S1 AND TRANSPLANT?
S5         15   S4 AND (MUTATE? OR MUTATION?)
S6         10   RD (unique items)
S7         21   S4 AND MUTANT?
S8         13   S7 NOT S5
S9         13   RD (unique items)
```

3/3,AB/1 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

14116400 BIOSIS Number: 01116400
Stimulating cell proliferation through the pharmacologic activation of c-kit
Jin L; Asano H; Blau C A
Mail Stop 357710, Health Sci. Build., Div. Hematol., Dep. Med., Univ. Washington, Seattle, WA 98195, USA
Blood 91 (3). 1998. 890-897.
Full Journal Title: Blood
ISSN: 0006-4971

RB145 A2 B56

3/3,AB/2 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

10000902 BIOSIS Number: 95000902
THE EFFECT OF THE IMMUNOPHILIN LIGANDS RAPAMYCIN AND FK506 ON PROLIFERATION OF MAST CELLS AND OTHER HEMATOPOIETIC CELL LINES
HULTSCH T; MARTIN R; HOHMAN R J
ALLERGIC DISEASES SECTION, LAB. CLINICAL INVESTIGATION, NATL. INST. ALLERGY INFECTIOUS DISEASES, NATL. INST. HEALTH, BETHESDA, MD. 20892.
MOL BIOL CELL 3 (9). 1992. 981-987. CODEN: MBCEE
Language: ENGLISH

QH601. C442

3236582 BIOSIS Number: 99236582
Calcineurin **mutants render T lymphocytes resistant to cyclosporin A**
Zhu D; Cardenas M E; Heitman J
Box 3546, 322 CARL Build., Research Drive, Duke Univ. Med. Cent., Durham, NC 27710, USA
Molecular Pharmacology 50 (3). 1996. 506-511.
Full Journal Title: Molecular Pharmacology
ISSN: 0026-895X
Language: ENGLISH
Print Number: Biological Abstracts Vol. 102 Iss. 010 Ref. 152212
Descriptors/Keywords: RESEARCH ARTICLE; JURKAT CELL LINE; PHARMACOLOGY; CYCLOSPORIN A; IMMUNOSUPPRESSANT-DRUG; RESISTANCE; TOXIC SIDE EFFECTS; FK506; IMMUNOSUPPRESSANT-DRUG; **CALCINEURIN ; MUTATION**
Concept Codes:

QP901. M65

6/3/7 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

10191299 EMBASE No: 96376115
Rethinking immunosuppression in terms of the redundant and nonredundant steps in the immune response
Halloran P.F.
Dr. P.F. Halloran, Division of Nephrology/Immunology, Department of Medicine, University of Alberta, 8249-114 Street, Edmonton, Alta. T6G 2R8 Canada
Transplantation Proceedings (USA) , 1996, 28/6 SUPPL. 1 (11-18)
CODEN: TRPPA ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGES: English

RD120.7.T68

6/3/9 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06336882 90081883
Sensitivity to cyclosporin A is mediated by cyclophilin **in Neurospora crassa and Saccharomyces cerevisiae.**
Tropschug M; Barthelmess IB; Neupert W
Institut fur Physiologische Chemie, Universitat Munchen, FRG.
Nature (ENGLAND) Dec 21-28 1989, 342 (6252) p953-5, ISSN 0028-0836
Journal Code: NSC
Languages: ENGLISH

6/3,AB/5 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04017035 Genuine Article#: QZ064 Number of References: 43
Title: A COMMON MUTATION IN THE HOMINOID CLASS-I A-LOCUS IFN-RESPONSIVE ELEMENT RESULTS IN THE LOSS OF ENHANCER ACTIVITY
Author(s): VALLEJO AN; ALLEN KS; PEASE LR
Corporate Source: MAYO CLIN & MAYO FDN,DEPT IMMUNOL/ROCHESTER//MN/55905;
MAYO CLIN & MAYO FDN,DEPT IMMUNOL/ROCHESTER//MN/55905
Journal: INTERNATIONAL IMMUNOLOGY, 1995, V7, N5 (MAY), P853-859
ISSN: 0953-8178
Language: ENGLISH Document Type: ARTICLE

7/3,AB/1 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06407564 Genuine Article#: YQ651 Number of References: 112
Title: Ligand- targeted **receptor-mediated vectors for** gene delivery
Author(s): Deonarain MP (REPRINT)
Corporate Source: UNIV LONDON IMPERIAL COLL SCI TECHNOL & MED,DEPT BIOCHEM/LONDON SW7 2AY//ENGLAND/ (REPRINT)
Journal: EXPERT OPINION ON THERAPEUTIC PATENTS, 1998, V8, N1 (JAN), P53-69
ISSN: 1354-3776 Publication date: 19980100
Publisher: ASHLEY PUBL LTD, 1ST FL, THE LIBRARY, 1 SHEPHERDS HILL HIGHGATE, LONDON, ENGLAND N6 5QJ
Language: English Document Type: REVIEW
05414244 Genuine Article#: VW756 Number of References: 190
Title: CANCER AND GENE-THERAPY
Author(s): SCHMIDTWOLF GD; SCHMIDTWOLF IGH
Corporate Source: HUMBOLDT UNIV BERLIN,VIRCHOW CLIN,DEPT INTERNALMED,DIV HEMATOL ONCOL,AUGUSTENBURGER PL 1/D-13353 BERLIN//GERMANY/; HUMBOLDT UNIV BERLIN,VIRCHOW CLIN,DEPT INTERNALMED,DIV HEMATOL ONCOL/D-13353 BERLIN//GERMANY/
Journal: ANNALS OF HEMATOLOGY, 1996, V73, N5 (NOV), P207-218
ISSN: 0939-5555
Language: ENGLISH Document Type: REVIEW
/3,AB/3 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04609781 Genuine Article#: TW450 Number of References: 38
Title: VECTORS AND TARGET-CELLS FOR GENE-THERAPY OF BLOOD-DISEASES
Author(s): QAZILBASH M; YOUNG N; LIU J
Corporate Source: NHLBI,NCI,MED BRANCH/BETHESDA//MD/20892; NHLBI,HEMATOL BRANCH/BETHESDA//MD/20892
Journal: TRENDS IN CARDIOVASCULAR MEDICINE, 1996, V6, N1 (JAN), P25-30
ISSN: 1050-1738
Language: ENGLISH Document Type: ARTICLE
7/3,AB/4 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04143651 Genuine Article#: RH464 Number of References: 177
Title: RECEPTOR-MEDIATED GLYCOTARGETING
Author(s): WADHWA MS; RICE KG
Corporate Source: UNIV MICHIGAN,COLL PHARM,428 CHURCH ST/ANN ARBOR//MI/48109; OHIO STATE UNIV,COLL PHARM/COLUMBUS//OH/43210
Journal: JOURNAL OF DRUG TARGETING, 1995IALOG(R)File 34:SciSearch(R) Cited Ref Sci

03817992 Genuine Article#: QJ249 Number of References: 71
Title: TARGETED VECTORS FOR GENE-THERAPY
Author(s): MILLER N; VILE R
Corporate Source: GLAXO INST MOLEC BIOL SA,14 CHEM AULX/CH-1228 GENEVA//SWITZERLAND/; ST THOMAS HOSP,RAYNE INST,IMPERIAL CANC RES FUND,CANC GENE THERAPY LAB/LONDON SE1 7EH//ENGLAND/
Journal: FASEB JOURNAL, 1995, V9, N2 (FEB), P190-199
ISSN: 0892-6638
Language: ENGLISH Document Type: REVIEW
03624532 Genuine Article#: PT948 Number of References: 49
Title: STRATEGIES TO ACHIEVE TARGETED GENE DELIVERY **VIA THE RECEPTOR-MEDIATED ENDOCYTOSIS PATHWAY**
Author(s): MICHAEL SI; CURIEL DT
Corporate Source: UNIV ALABAMA,LUREEN B WALLACE TUMOR INST 620,1824 6TH AVE S/BIRMINGHAM//AL/35294; UNIV ALABAMA,CTR COMPREHENS CANC,DEPT BIOCHEM &MOLEC GENET/BIRMINGHAM//AL/35294; UNIV ALABAMA,CTR COMPREHENS CANC,GENE THERAPY PROGRAM/BIRMINGHAM//AL/35294
Journal: GENE THERAPY, 1994, V1, N4 (JUL), P223-232
ISSN: 0969-7128

/3,AB/48 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

9811773 EMBASE No: 95367702
Crystal structures **of human** calcineurin **and the human FKBP12-** FK506 - calcineurin **complex**
Kissiner C.R.; Parge H.E.; Knighton D.R.; Lewis C.T.; Pelletier L.A.; Tempczyk A.; Kalish V.J.; Tucker K.D.; Showalter R.E.; Moomaw E.W.; Gastinel L.N.; Habuka N.; Chen X.; Maldonado F.; Barker J.E.; Bacquet R.; Villafranca J.E.
Agouron Pharmaceuticals Inc., 3565 General Atomics Court, San Diego, CA 92121-1121 USA
Nature (United Kingdom) , 1995, 378/6557 (641-644)
CODEN: NATUA ISSN: 0028-0836
LANGUAGES: English SUMMARY LANGUAGES: English
Title: STRUCTURE-ACTIVITY STUDIES OF RAPAMYCIN ANALOGS - EVIDENCE THAT THE C-7 METHOXY GROUP IS PART OF THE EFFECTOR DOMAIN AND POSITIONED AT THE FKBP12-FRAP INTERFACE
Author(s): LUENGO JI; YAMASHITA DS; DUNNINGTON D; BECK AK; ROZAMUS LW; YEN HK; BOSSARD MJ; LEVY MA; HAND A; NEWMANTARR T; BADGER A; FAUCETTE L; JOHNSON RK; DALESSIO K; PORTER T; SHU AYL; HEYS R; CHOI JW; KONGSAEREE P; CLARDY J; HOLT DA
Corporate Source: SMITHKLINE BEECHAM PHARMACEUT,DEPT MED CHEM,709SWEDELAND RD/KING OF PRUSSIA//PA/19406; SMITHKLINE BEECHAM PHARMACEUT,DEPT CELLULAR BIOCHEM/KING OF PRUSSIA//PA/19406; SMITHKLINE BEECHAM PHARMACEUT,DEPT BIOMOLEC DISCOVERY/KING OF PRUSSIA//PA/19406; SMITHKLINE BEECHAM PHARMACEUT,DEPT PROT BIOCHEM/KING OF PRUSSIA//PA/19406; SMITHKLINE BEECHAM PHARMACEUT,DEPT SYNTHET CHEM/KING OF PRUSSIA//PA/19406; CORNELL UNIV,DEPT CHEM/ITHACA//NY/14853
Journal: CHEMISTRY & BIOLOGY, 1995, V2, N7 (JUL), P471-481
ISSN: 1074-5521
Language: ENGLISH Document Type: ARTICLE

2/3/11 (Item 11 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

10615437 BIOSIS NO.: 199699236582
Calcineurin mutants render T lymphocytes resistant to cyclosporin A.

AUTHOR: Zhu Dahai; Cardenas Maria E; Heitman Joseph(a)
AUTHOR ADDRESS: (a)Box 3546, 322 CARL Build., Research Drive, Duke Univ. Med. Cent., Durham, NC 27710, USA

JOURNAL: Molecular Pharmacology 50 (3):p506-511 1996
ISSN: 0026-895X

2/3/16 (Item 16 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

10044014 BIOSIS NO.: 199598498932
Mutations **that perturb** cyclophilin **A ligand binding pocket confer cyclosporin A resistance in Saccharomyces cerevisiae.**

AUTHOR: Cardenas Maria Elena; Lim Eric; Heitman Joseph(a)
AUTHOR ADDRESS: (a)Dep. Genetics, Duke Univ. Med. Cent., Box 3546, 322 Carl Build., Research Drive, Durham, NC 2771, USA

JOURNAL: Journal of Biological Chemistry 270 (36):p20997-21002 1995
ISSN: 0021-9258

2/4/24 (Item 24 from file: 5)
FN- DIALOG(R)File 5:BIOSIS PREVIEWS(R)|

AZ- 07685926|
AA- 000092032847|
TI- A SINGLE TRP-121 TO ALA-121 MUTATION **IN HUMAN** CYCLOPHILIN ALTERS **CYCLOSPORIN A AFFINITY AND PEPTIDYL-PROLYL ISOMERASE ACTIVITY|**
AU- BOSSARD M J; KOSER P L; BRANDT M; BERGSMA D J; LEVY M A|
CS- DEP. MED. CHEM., SMITHKLINE BEECHAM PHARMACEUTICAL, KING OF PRUSSIA, PA. 19406.|
JN- BIOCHEM BIOPHYS RES COMMUN|
JN- Biochemical and Biophysical Research Communications|
SO- 176 (3). 1991. 1142-1148.|

5/3/18 (Item 1 from file: 351)
DIALOG(R)File 351:DERWENT WPI

011762531 **Image available**
WPI Acc No: 98-179441/199816
XRAM Acc No: C98-057742
XRPX Acc No: N98-141902
Selective inhibition of proliferation of haematopoietic cells - using macrolide binding proteins and analogues, useful for treatment of graft versus host disease
Patent Assignee: HARVARD COLLEGE (HARD); UNIV LELAND STANFORD JUNIOR (STRD)
Inventor: BELSHAW P J; **CRABTREE G** ; SCHREIBER S L
Number of Countries: 075 Number of Patents: 002
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Main IPC	Week
WO 9808956	A2	19980305	WO 97US15153	A	19970827	C12N-015/54	199816 B
AU 9741672	A	19980319	AU 9741672	A	19970827	C12N-015/54	199831

Priority Applications (No Type Date): US 9624666 A 19960827
Filing Details:

Patent	Kind	Filing Notes	Application	Patent
WO 9808956	A2			

Designated States (National): AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV